Amendments to the Figures

The attached sheet of drawings includes changes to sheet 18 which shows Figure 18. This sheet replaces original sheet 18 and original Figure 18. In replacement sheet 18, the sequence shown in Figure 18 has been amended as follows:

Insert "Q" as amino acid 41;

Insert "Y" as amino acid 471; and

Insert "N" as amino acid 891.

Attachment: Replacement Sheet

Annotate Sheet Showing Changes

Remarks

Claims 1-5, 7-12, 14-19 and 21-38 are pending in the application, with claims 22-38 being withdrawn. Claims 6, 13 and 20 have been canceled without prejudice or disclaimer.

Sequence Listing Statements

The substitute sheets of the sequence listing submitted herewith include no new matter. The substitute copy of the computer readable form of the sequence listing is the same as the substitute paper copy of the sequence listing submitted herewith.

Miscellaneous - Substitute Figure 18 and the Substitute Sequence Listing

SEQ ID NO: 1, in the sequence listing, and as shown on Figure 18, has been amended without adding new matter as follows:

Insert ""Q" as amino acid 41;

Insert "Y" as amino acid 471; and

Insert "N" as amino acid 891.

The artisan would recognize that there was a clear error in Figure 18. In the figure, each row is numbered to contain 60 amino acids in 6 blocks of 10 amino acids each. However, three of the "blocks" that should contain ten amino acids instead only contain nine amino acids. Specifically, the fifth block in line 1 only has nine amino

acids in it, as does the last block in each of rows 8 and 15. The sequences in the other blocks are not affected.

Support for this amendment is found in the specification. First, the sequence is identified with specificity in the specification. At specification page 8, in the legend to Figure 18, and on Figure 18, it is stated that SEQ ID NO:1 is the amino acid sequence of mature *Homo* sapiens Ephrin type-B receptor 4 (EphB4).

Second, reference is given to the sequence that was known in the art at that time. On specification page 9, lines 1-2, it is stated that the placement of the domains shown in Figure 19 relative to the EphB4 amino acid sequence is based on information taken from the most recent report from NCBI Accession number NP_004435. NCBI Accession number NP_004435 is the sequence of the ephrin receptor EphB4 precursor.

Third, NCBI NP_004435 version 2 (Exhibit A) which shows those three amino acids was the version available at the time of filing of Applicant's priority document on September 16, 2002. In the comment section of version 2, it is stated that version 2 replaced gi:4758290 (which was version 1) on December 21, 2001. Exhibit B is version 3. In the comment section of version 3, it is stated that version 3 did not replace version 2 until July 11, 2003, after the filing of the priority document (but before the September 9, 2003 filing date of the PCT application). Thus, version 2 was the version available on September 16, 2002 and version 3 was the version available on September 9, 2003.

Fourth, both NCBI versions 2 and version 3 contain these three amino acids.

Fifth, the artisan would recognize there was an error because the numbering of the lines clearly indicates that 10 amino acids should be present in each block but only nine amino acids were listed in the three indicted blocks. Also, the correction would be

easily and clearly obtainable from the sequence that was known in the art at that time. A comparison of the sequence of Figure 18 and SEQ ID NO:1 with the NCBI sequence version 2 and version 3 shows clearly that there should be a "Q" as amino acid 41, a "Y" as amino acid 471; and an "N" as amino acid 891. Accordingly, Applicant respectfully asserts that this amendment is not new matter and that the artisan would recognize the error in the drawing and SEQ ID NO:1.

The Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

At Office action page 3, claims 1-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner states that the claims are drawn to a method for inhibiting the proliferation of a cancer cell and that the claims read on a method of preventing or treating cancer in a subject. The Examiner states that the claims are not enabled because the teachings represent insufficient guidance and objective evidence to predictably enable the use of the claim invention, and that thus, the claims are not enabled for a method of preventing or treating cancer in a subject.

The Examiner states that the art of anti-cancer therapy is highly unpredictable, relying on Gura (Science *278*:1041-1042(1997) and Kaiser (Science *313*: 1370 (2006)).

The Examiner states that the treatment of disease with antibodies in vivo is generally unpredictable, relying on White et al. (Annu. Rev. Med. *52:*125-145 (2001) and on Young (U.S. patent application pub 20004180002).

The Examiner generally argues that in vitro demonstration of anti-cancer activity does not routinely indicate anti-cancer efficacy in vivo. Following from this, the

Examiner has rejected all claims in the present application on the basis that there is no data that show that EphB4-binding antibodies have any anti-cancer activity in vivo. The Examiner thus concludes that the specification is not enabling for claims to methods of treating or preventing cancer in a subject.

In addition, the Examiner has also specifically stated that any data relating to the treatment of cancer using a particular agent do not necessarily suggest that the same agent is also useful for the prevention of cancer. Thus, the Examiner concludes that in the absence of any data relating to cancer prevention using an EphB4 antibody, the Examiner has alleged that the claims (insofar as they relate to cancer prevention) are also not enabled.

Applicant respectfully traverses this rejection.

In response to this rejection, we would first like to point out to the Examiner that the use of antibodies in the treatment of cancers is well known in the art. For example the reviews of Bodey (*Expert Opin Biol Ther. 1(4)*: 603-17, 2001), Hudson (*Curr Opin Immunol. 11(5)*: 548-57, 1999) and Cragg et al. (*Curr Opin Immunol. 11(5)*: 541-7, 1999) all describe the use of antibodies in the treatment of cancers. In light of the above, we submit that the teaching of the present specification (in conjunction with what is known in the art) would readily enable a person skilled in the art to perform methods for the treatment or prevention of cancer using an antibody or antigen binding portion thereof directed to an epitope located within residues 200 to 400 of EphB4.

However, we note that the Examiner's objection also appears to be predicated on an allegation that the in vitro data presented in the specification does not necessarily indicate that the claimed methods will be useful for the treatment of cancer on the basis

that in vitro demonstration of anti-cancer activity (for example as set out in the present specification) does not routinely indicate anti-cancer efficacy in vivo. Our comments in response to this aspect of the rejection are set out below.

Until 1985 the US National Cancer Institute provided screening support to cancer research for the selection of compounds for further preclinical and clinical development, predominantly using in vivo tumor models. However, due to general dissatisfaction with the performance of prior in vivo primary screens, in 1984 an in vitro primary anti-cancer drug screen was presented by Professor Michael R. Boyd (currently Abraham Mitchell Chair and Director and Professor of Medicine and Pharmacology, USA College of Medicine) as an alternative to this. By 1990 the in vitro screen was fully established and had replaced the in vivo screens. The in vitro assay involves treatment of monolayers of panel cell lines in 96-well plates incubated with the test agents at various dilutions (typically 10^{-4} to 10^{-8} M) for 48 h. Cells are then fixed, stained and counted.

As set out in the specification, the present inventors used an in vitro screen substantially equivalent to the in vitro screen described above to test the antibodies to EphB4.

The assays used to test the EphB4 antibody and define the functional epitope in accordance with the present invention are accepted in the field as indicators of in vivo growth and metastatic potential and have been used successfully to screen many different anti-cancer agents. Thus, we submit that a person skilled in the art could reasonable assume that the data presented in the present specification are indicative of a successful in vivo cancer treatment.

In support of the above assertion, we also direct the Examiner's attention to US patent publication US 20050084873. US 20050084873 was published after the priority date of the present application and US 20050084873 also claims a later priority date than the present application.

US 20050084873 presents data showing that antibodies targeting epitopes in the extracellular domain of EphB4 not only inhibit tumor growth but cause regression of established tumors in a xenograft mouse model of a head and neck cancer (see Figure 60 of the '873 publication). To generate the data in US 20050084873, tumors using the cell line SCC15 were allowed to establish for 4 days then treated on alternate days for 14 days with IP or SC (no differences were noted) with 40 mg/kg of two different EphB4 antibodies in separate experiments. Tumors treated with each antibody individually showed a significant decrease in tumor size compared to control (PBS) treated tumors. As set out above, we submit that such anti-cancer activity could be predicted on the basis of the in vitro data set out in the present specification.

The Examiner also specifically alleged that the data presented in the subject specification does not support claims to the prevention of cancer.

However, US 20050084873 also presents data showing that antibodies targeting epitopes in the extracellular domain of EphB4 significantly prevent the growth of SCC15 tumors in nude mice (Figure 58 of US 20050084873 of the '873 publication). In this study, 2.5 $x10^6$ tumor cells were premixed with Matrigel, +/-VEGF and individual antibodies before subcutaneous injection into mice. Tumor size was measured after 14 days and two antibodies significantly reduced the size of the tumors in comparison to the control (PBS) treated tumors.

In summary, we submit that the data presented in the subject specification clearly provide sufficient guidance and objective evidence to predictably enable the use of the claimed invention, specifically methods for the treatment and/or prevention of cancer. As set out above, not only does the specification provide such guidance and evidence, but later research (eg. the disclosure of US 20050084873) further supports the teachings of the present invention with additional supporting evidence. Accordingly, Applicant respectfully requests withdrawal of this enablement rejection.

The Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

At Office action page 8, claims 5-7, 12-14 and 19-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner states that the rejected claims are drawn to a genus of EphB4 peptides having a sequence at least 85% identical to residues selected from the recited list, but that the specification discloses only one purified EphB4 protein with a sequence of SEQ ID NO: 1.

In short, this rejection relates to the recitation of peptides having 85% or 90% identity to regions of the EphB4 sequence set forth in SEQ ID NO: 1. As the Examiner has noted, EphB4 polypeptide (SEQ ID NO: 1) is disclosed in the specification. Thus, the Examiner has alleged that the inventors was not in possession of the EphB4 variants covered in these claims at the time of filing the patent application.

Applicant respectfully traverses this rejection.

In response to this objection, and to expedite allowance, Applicant as amended the claims to simply remove the homology thresholds recited in the claims. Specifically,

applicant has deleted the phrase "...at least 85% identical to residues..." from the fourth line in each of claims 5, 12 and 19. In addition, applicant has deleted claims 6, 13 and 20.

Accordingly, it is believed that this rejection may be withdrawn.

Conclusion

Prompt and favorable consideration of this Amendment and Reply is respectfully requested. Applicant believes the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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